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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/728,028	12/03/2003	Francine Gervais	NBI-139CP	8334
959	7590	11/17/2006		
LAHIVE & COCKFIELD, LLP ONE POST OFFICE SQUARE BOSTON, MA 02109-2127			EXAMINER SAMALA, JAGADISHWAR RAO	
			ART UNIT	PAPER NUMBER
			1618	
DATE MAILED: 11/17/2006				

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b> 10/728,028	<b>Applicant(s)</b> GERVAIS ET AL.	
	<b>Examiner</b> Jagadishwar R. Samala	<b>Art Unit</b> 1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☐ Responsive to communication(s) filed on \_\_\_\_.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 1-105 is/are pending in the application.  
4a) Of the above claim(s) 3-20,24-30,34-42,46-101 and 103-105 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-2,21-23,31-33,43-45 and 102 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a) ☐ All    b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

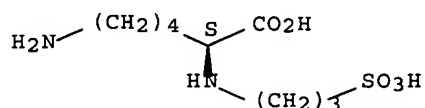
\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)                                | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. ____. |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                       | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date ____. | 6) <input type="checkbox"/> Other: ____.  |

**DETAILED ACTION*****Election Acknowledged***

1. Applicant's election with partial traverse the invention group I of claims 1-39,43-47,49, 50 and 102 and election of species (i.e. alpha-N-(3-sulfopropyl)-L-Lysine) is acknowledged.



Although applicant indicated that claims 1-2,8-9,13,18,21-23,31-33,43-45,51-54,55-63,65-67,69,75-76,95-98, and 100-105 read on the elected species, based on species elected, examiner will choose formula of claim 31 a subgenus formula and its dependent claims for the examination purpose. And the claim 8,9, 13 and 18 will be with drawn from the consideration, until further explanation is provided. However, the formula recited in claim 31 and formula II and IV recited in 13 and claims 8,9, and 18 may or may not be necessarily contain overlapping the scope. Proper description and explanation is required to teach how elected species above are related to these said formulas II and IV. Applicant's partial traverse the restriction requirement on the grounds that they are not patentably distinct because the method of diagnosing cannot be practiced without the invention of group I. However this argument is not persuasive

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because each invention is patentably distinct to each other as evidenced by numerous patents (see US 6,096,782, US 6,191,166 and 2001/0020087). The etiology of the Alzheimer's disease is virtually unknown but has been variously attributed to viruses, toxins, concentrations of heavy metals, as well as genetic defects. For example, Alzheimer's disease (amyloid disease) can be diagnosed by polypeptide and antibodies and nucleotide probes corresponding thereto for use in diagnostic tests as shown in US patent (US 4,666,829, 6,207,856 and 6,211,235), and thus the searches for all inventions are burdensome. For the reasons above, inventions of group I and II are found to be patentably distinct, and therefore, the restriction requirement is maintained, and made FINAL. And thus, the invention for group II (40-42, 48, 51-102 and 103-105) will not be included to examine for the reasons set forth above.

2. Claims 1-2 21-23,31-33,43-45, and 102 will be presented for examination.

### ***Claim Disposition***

3. Claims 1-105 are pending and 1-2 21-23,31-33,43-45, and 102 will be presented for examination.

***Claim Rejections - 35 USC § 112***

Claim 1-2 21-23,31-33,43-45, and 102 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making certain amyloid-targeting imaging agent of formula recited in claim 31 such as elected species, does not reasonably provide enablement for any type of amyloid targeting imaging agents which contain all the possible substituents at any positions of  $R^1$ ,  $R^2$  and T, as suggested by the breadth of the instant claims, to be employed in the diagnosis of amyloid diseases of the instant invention. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to the invention commensurate in scope with these claims. Accordingly, the examiner purports that it would constitute undue experimentation to determine what compounds can be effectively employed as a amyloid-targeting imaging agents as per the parameters of the instant claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are

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weighed, it is examiner's position that one skilled in the art could not practice the invention without undue experimentation.

(1) Nature of the invention

The claims are directed to an amyloid-targeting imaging agents capable of crossing blood-brain barrier for the diagnosis of amyloid diseases.

(2) The state of prior art

There are no known compounds or imaging agents of similar structure which have been demonstrated to treat or prevent all amyloid diseases due to degenerative brain disorder characterized clinically by progressive loss of memory, confusion, reasoning, judgment and emotional stability that gradually leads to profound mental deterioration. Until this time, there has been no useful diagnostic test for Alzheimer's disease. Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits. The existence of such an "amyloid-targeting imaging agent" is contrary to our present understanding of oncology. A definitive diagnosis is possible only postmortem or during life through a brain biopsy to reveal the presence of the characteristic neurotic plaques, tangles and cerebrovascular deposits which characterize the disorder. Thus, it is beyond the skilled artisan today to get an imaging agent to be effective against amyloid diseases.

(3) The relative skill of those in the art

The relative skill of those in the art of pharmaceuticals is high. As seen in Audia et al., (US 6,096,782) which discloses various compounds which inhibit  $\beta$ -amyloid

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peptide release and/or its synthesis and useful in the prevention or treatment of patients with AD in order to inhibit further deterioration of their conditions. Potter (US 6,214,569) discloses a method of screening for compounds which suppress the formation of Alzheimer  $\beta$  -protein filaments in the presence of promoting factors and which suppress the neurotoxic effects.

(4) The predictability or unpredictability of the art

The specification does not provide any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant compounds.

Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved".

See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

(5) The breadth of the claims

The instant claims embrace to an amyloid-targeting imaging agents capable of crossing blood-brain barrier for the diagnosis of amyloid diseases. The instant claims cover "Amyloid diseases" that are known to exist for which there is no enablement provided.

The breadth of the claims is further exacerbated by the instantly claimed plethora of compounds that are described as being amyloid-targeting imaging agents or prodrug thereof represented by compounds of Formula I or II.

(6) The amount of direction or guidance presented

The instant disclosure provides guidance through the examples and the disclosure of the specification sufficient direction for the use of amyloid-targeting agents. Although the specification and disclosure provide enabling disclosure for making certain amyloid-targeting imaging agents (e.g. elected species) or compounds combined by claim 31, none of the specification or the disclosure provides enabling disclosure for making all types of imaging agents as claimed and or for all types of imaging agents possibly known in the art, there is insufficient evidences for the claimed use of amyloid-targeting agents in preventing or eliminating of said amyloid diseases, and for enablement in making/using vast number of possible compounds and the genus of formula I for the treatment or prevention of said amyloid diseases that may or may not related to genetic defects. The specification provides no guidance, in the way of enablement for the full scope of all compounds of formula I or II that are potentially suitable for the invention work similarly as to amyloid-targeting imaging agents. The skill artisan would have not known that which compounds of the claimed compounds of formula I or II are capable of accomplishing the desired result of the claimed invention without undue amount of experimentation.

(7) The presence or absence of working examples

As stated above, the specification and disclosure only provide the usefulness of amyloid-targeting imaging agents in diagnosis of amyloidotic diseases. Both specification and the disclosure fail to provide adequate representation regarding the conclusion of the efficacy of amyloid-targeting imaging agents in treating or screening (diagnosis) all amyloid diseases due to degenerative brain disorders from applicant's



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showing of the efficacy of amyloid-targeting moiety in preventing or inhibiting amyloid protein assembly into insoluble fibrils which, in vivo are deposited in various organs.

(8) The quantity of experimentation necessary

Since the efficacy of amyloid-targeting moiety in preventing or inhibiting amyloid protein assembly mentioned above cannot be predicted from a priori but must be determined from the case to case by painstaking experimental study and when the above factors are weighed together, one of ordinary skill in the art would be burdened with undue "painstaking experimentation study" to use the invention commensurate in scope with the claims.

#### ***Allowable Subject Matter***

Election of species (i.e. alpha-N-(3-sulfopropyl)-L-Lysine) is allowable. The following is a statement of reasons for the indication of allowable subject matter: The closest prior art, Audia et al (US 6,096,782 and US 6,191,166) and Potter (US 6,214,569) neither alone or in combination discloses or fairly suggest producing the compounds set forth for diagnosis/screening amyloid diseases by administering to the patient a therapeutically effective dose of a compound which interferes with the interactions between Alzheimer  $\beta$  -protein and Apolipoprotein E4 or  $\alpha$ 1 -antichymotrypsin, thereby suppressing the formation of Alzheimer  $\beta$  -protein filaments and the neurotoxic effects of these filaments. Thus diagnosis or screening of amyloid diseases using specific imaging agent

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as claimed (i.e.) has not been known to the state of the art nor it is not obvious over prior art of the state.

Claims which are drawn to election of species, would be allowable if rewritten to overcome the rejections(s) under 35 U.S.C. 112 1<sup>st</sup> paragraph, set forth in this Office action.

### ***Conclusion***

At present no claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jagadishwar R. Samala whose telephone number is (571)272-9927. The examiner can normally be reached on 8.30 A.M to 5.00 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Hartley can be reached on (571)272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

sjr

Jagadishwar R Samala  
Examiner  
Art Unit 1618



**VICKIE KIM**  
**PRIMARY EXAMINER**